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Serial No. 10/738,413 Docket No. SC66U-US

REMARKS

Claims 1-41 are pending after entry of this paper. Claims 1-39 have been rejected. Claims 40 and 41 have been withdrawn. Applicants reserve the right to pursue withdrawn claims in a divisional or continuing application.

Claims 1 and 3 have been amended to delete the term, "prevent" in order to address the Examiner's concerns. Similarly, claim 31 has been amended to delete the term, "preventing."

Furthermore, claims 1 and 3 have been amended to delete the term, "or other unwanted skin condition" in order to address the Examiner's concerns.

Applicants respectfully acknowledge the examination of claim 39 with the elected Group I claim, 1-38.

No new matter has been introduced by these amendments. Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

Response to Rejections under 35 U.S.C. §112

Claims 1-39 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Applicants respectfully disagree and request reconsideration of this rejection.

The Examiner contends that applicants have not provided a particular model that is recognized as correlating siRNA oligomers specific for mouse and human tyrosinase mRNA to the desired effect on the broad genus of conditions that are instantly recited. According to MPEP 2164.02, an *in vitro* or *in vivo* animal model example in the specification constitutes a

"working example" if it "correlates" with a disclosed or claimed method invention. That section also states that a particular model should be accepted as correlative if the state of the prior art recognizes it as correlating to a specific condition. Moreover, as the Examiner is well aware, "use of *in vitro* experiments to establish *in vivo* events is, in principle, a valid methodology." *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985); *Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA 1980).

Here, the instant specification describes a Northern Dot Blot experiment to measure tyrosinase mRNA in a B16 mouse melanoma cell line after 48-hour treatment with a tyrosinase siRNA *in vitro* (*see* page 17, [0069], and Figure 1). The B16 cell line, which is originally derived from melanomas in mice, represents actual melanoma tumors that would be found in live mice. In other words, applicants' *in vitro* testing reflects the events as they would occur *in vivo*. As such, the *in vitro* data provided in the instant specification demonstrates the effectiveness of tyrosinase siRNA *in vivo*. Additionally, this *in vitro* testing method represents an effective way to test the tyrosinase siRNA molecules *in vivo* on a large scale. Therefore, applicants maintain that the *in vitro* model in the instant specification correlates siRNA oligomers specific for mouse and human tyrosinase mRNA to the *in vivo* treatment of hyperpigmentation orders and other unwanted pigmentation, as recited in the claims, because it constitutes a valid methodology for establishing such *in vivo* events.

The specification further states that the prior art includes skin lightening agents, including hydroquinone and vitamin C, which "typically lighten the skin by inhibiting the expression of tyrosinase enzymes." (*see* page 2, para. [0004]. Thus, the prior art recognizes that inhibition of tyrosinase expression occurs *in vivo* and provides a nexus between tyrosinase expression and hyperpigmentation. Therefore, the prior art recognizes that the instant

specification teaches one skilled in the art how to make and use the invention with a reasonable amount of guidance to obtain the desired effects claimed.

The Examiner also argues that applicants have not provided any correlation between the instant method and a result that prevents or eliminates unwanted skin conditions as instantly recited. Additionally, the Examiner states that the applicants failed to show that introduction of a siRNA oligomer specific for tyrosinase would prevent unwanted pigmentation. Applicants respectfully disagree. However, in order to advance prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have deleted the term "prevent" from claims 1 and 3, and the term "preventing" from claim 31.

The Office Action states that the specification is not enabling for the treatment, amelioration, reduction and/or elimination of a vast genus of disorders by administering a broad genus of siRNA oligomers. However, as the Examiner is well aware,

> not everything necessary to practice the invention need be disclosed. In fact what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further, the scope of enablement must only bear a 'reasonable correlation' to the scope of the claims.

MPEP 2164.08, 8th ed., Rev. 4: pg. 2100-205, col. 2, para. 1.

Applicants assert that the instant specification provides sufficient guidance for one skilled in the art to make and use the claimed invention commensurate in scope with the claims. Specifically, the instant specification provides techniques for synthesizing siRNA molecules, all of which are known to those of skill in the art (*see* page 8, para. [0040] to para. [0042]). Furthermore, the specification describes various formulations and targeted delivery systems by which the siRNA molecules can be effectively administered to more readily reach

and affect the skin cells (*see* page 10, para. [0046]; page 11 to page 12, para. [0049] to para. [0052]). The specification states that the determination of an effective dose or amount of the compositions is well within the capability of those skilled in the art (*see* page 10, para. [0048]). Additionally, the specification provides test results from a Northern Dot Blot experiment that measured the amount of tyrosinase mRNA in B16 mouse melanoma cell line after treatment with a tyrosinase siRNA for 48 hours (see page 17, para [0069]; Figure 1). Not only would one skilled in the art be able to replicate this experiment, this *in vitro* system provides a reasonable correlation to an *in vivo* system, which is encompassed by the scope of the claims. Thus, contrary to the Examiner's contention, the instant specification provides one skilled in the art with a reasonable amount of guidance to make and use the full scope of the claimed invention.

The Examiner contends that a connection between inhibiting expression of a target gene by RNA interference *in vivo* is unpredictable. Specifically, the Examiner relies on two publications by Caplen., et al. to support the unpredictability of nucleic acid delivery *in vivo*. Applicants respectfully disagree for the following reasons. First, the Caplen, et al. publication (*Gene*, 252, pp. 95-105, 2000) does not refer to nor suggests that there is any unpredictability of inhibiting tyrosinase expression via RNAi, which is the focus of the instant invention. Second, the subject of Caplen, et al. (*Expert Opin Biol Ther.*, 3, pp. 575-86, 2003) is inapplicable to the instant invention because it discusses RNA interference as a potential gene therapy approach for cancer and infectious disease, not hyperpigmentation disorders, as instantly claimed. Moreover, Caplen (2003) distinguishes RNA interference over previous gene therapy technologies as an advantageous method for the downregulation of gene expression. Therefore, the Caplen references do not call into question the predictability in the outcome of the claimed invention.

The Examiner also points to Zhang, et al. (*Curr Pharm Biotechnol.*, 5, pp. 1-7, 2004) for further support that siRNA delivery to mammalian cells is unpredictable. Zhang, however, teaches other forms by which siRNA oligomers specific for tyrosinase can be administered, and fails to discuss topically administering compositions containing siRNA oligomers specific for tyrosinase, which is the focus of the instant claims. Moreover, despite stating that effective delivery of siRNAs to mammalian cells "will not be so simple," Zhang in fact demonstrates that effective delivery of siRNA to mammalian cells can be achieved (*see, e.g.*, page 5, column 2, lines 14-19). Therefore, applicants maintain that Zhang, in fact, supports the enablement of the present claims in so far as it illustrates effective delivery of siRNA to mammalian cells.

The Examiner contends that the instant claims are directed to treating any unwanted pigmentation or any unwanted skin condition, not just hyperpigmentation. Specifically, the Examiner argues that Hartmann, et al. (*Drugs*, 64, pp. 89-107, 2004) allegedly illustrates the unpredictability of treating hypopigmentary disorders, which is "commensurate in scope with the instant claims" (*see* Office Action, page 6). Hartmann teaches various therapies for treating hypopigmentary disorders, such as phototherapy, synergistic drugs, and use of punch grafts. However, Hartmann fails to teach the use of siRNA molecules to inhibit tyrosinase expression for the treatment of any skin disorder, let alone hypopigmentation. Furthermore, Hartmann defines hypopigmentary disorders as those characterized by a "diminution of melanocytes in number and/or size (which could include up to a complete absence) or a reduction of melanin synthesis..." (Hartmann, et al., page 90).

In contrast, the claims of the instant invention, as amended, are directed to the treatment of hyperpigmentary disorders. Support may be found throughout the instant

specification, for example, at page 6, paragraph [0028]. Thus, contrary to the Examiner's argument, Hartmann is not analogous to the current invention because Hartmann refers to skin disorders caused by a lack of pigmentation, not unwanted pigmentation to which the instant claims are focused.

In view of the above arguments and amendments, applicants respectfully request reconsideration and withdrawal of §112, first paragraph rejections, to claims 1-39.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application. Favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. 50-3782, Order No. SC66U-US.

Respectfully submitted,

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